Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Transparencies from Workshop: Proposition 65 Listings via the Authoritative Bodies Mechanism

June 1998

A workshop was conducted on June 11, 1998, by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) to discuss issues related to the implementation of the authoritative bodies mechanism for listing under Proposition 65. The workshop was held at the International House, on the University of California, Berkeley, campus. Some of agenda items began with presentations by state staff to provide a background and context for the discussion. This package, which is being sent to workshop participants, contains copies of the transparencies used by state staff in making their presentations. The agenda was developed, in part, from comments received from interested parties. Agenda items were for discussion; some changes to the process or regulation may not be advisable or legally permissible.

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Workshop Agenda

Workshop Chair: Val Siebal, Chief Deputy Director, OEHHA

9:00 **Welcome**
Joan E. Denton, Director, OEHHA

Goals and objectives of the workshop
Val Siebal, Chief Deputy Director, OEHHA

9:15 **Legal aspects of authoritative bodies implementation**
Ed Weil, Deputy Attorney General (20 min.)
- Proposition 65 statutory requirements and overview of 22 CCR 12306
- Criteria for formal identification
- Legal requirements when authoritative bodies' findings differ
- Toxic Release Inventory litigation

Public discussion and comment

10:15 **BREAK**

10:30 **Designating authoritative bodies**
Lauren Zeise, Chief, OEHHA Reproductive and Cancer Hazard Assessment Section (RCHAS) (15 min.)
Public discussion and comment on issues, for example
- Whether there is a need to establish general criteria for authoritative body designations
- To what extent does expert peer review function in the decision to confer authoritative body designations
- Whether designations should be re-reviewed and, if so, under what circumstances

11:30 **Existing authoritative bodies**
Martha Sandy, Chief, OEHHA RCHAS Cancer Unit (20 min.)
Public discussion and comment on issues, for example
- Authoritative bodies' expertise and processes utilized in their determinations
- Application of 12306 guidance
- The possible need for greater definition of specific activities as authoritative within a large organization, such as US EPA
- US EPA's Toxic Release Inventory

12:30 **LUNCH**

1:30 **Continuation of discussion on existing authoritative bodies**

3:30 **BREAK**

3:45 **Other bodies suggested by the public for designation as "authoritative"**

Marlissa Campbell, OEHHA RCHAS Reproductive Toxicology Unit (5 min.)

Suggestions from the public:

- Agency for Toxic Substances and Disease Registry
- International Programme on Chemical Safety
- Health Environment Canada

Discussion and public comment on issues, such as the nature of potential conflicts among existing and potential authoritative bodies

Next steps concerning designation of authoritative bodies

4:15 **Scientific criteria for "as causing cancer or reproductive toxicity" in 22 CCR 12306**

Jim Donald, Chief, OEHHA RCHAS Reproductive Toxicology Unit (10 min.)

Discussion and public comment

5:15 **Public comment on additional issues related to the authoritative bodies listing mechanism**

5:30 **Next steps**

ADJOURN

Workshop presentation - "Designating authoritative bodies"

Lauren Zeise, Chief, OEHHA Reproductive and Cancer Hazard Assessment Section

Proposition 65 Statute

"A chemical is known to the state to cause cancer or reproductive toxicity if …

in the opinion of the state's qualified experts is has been clearly shown … to cause cancer or reproductive toxicity, or

a body considered to be authoritative by such experts has formally identified it as causing cancer or reproductive toxicity, or

an agency of the state or federal government has formally required it to be labeled or as causing cancer or reproductive toxicity"

(added to Health and Safety Code by 1986 General Election)

California Code of Regulations. Title 22.

12305 (b) "… the DART Committee may undertake the following activities:

> … (2) Identify bodies which are considered to be authoritative and which have formally identified reproductive toxicants…"

12306 (b) "the DART Committee shall have the authority to revoke or rescind any determination that a body is authoritative on the grounds that the respective Committee no longer considers the body to have expertise in the identification of chemicals as causing … reproductive toxicity"

State's Qualified Experts and Authoritative bodies designations

Oct 87	Scientific Advisory Panel (SAP) decision not to designate ABs
June 88	Lawsuit on failing to consider designations
April 89	Lawsuit settlement – SAP to formally consider AB designations
Summer 89	Public hearing on AB implementing regulations (22 CCR 12306)
Oct 89	SAP reviews 22 CCR 12306; SAP designates US EPA, IARC, NTP
April 90	SAP designates FDA, NIOSH

12306 Criteria an Authoritative Body Must Meet

1 It must be an agency or formally organized group

2 It must use a method to identify chemicals as causing cancer or reproductive toxicity provided in the Title 22 regulation

3 The State's qualified experts identify the body as having expertise in the identification of chemicals as causing cancer

Workshop presentation - "Existing authoritative bodies"
Martha Sandy, Chief, OEHHA RCHAS Cancer Unit

US ENVIRONMENTAL PROTECTION AGENCY

Chemicals listed under Proposition 65 through the authoritative bodies mechanism:

US EPA is the sole basis for listing:	**55**
US EPA is the partial basis for listing:	**5**

OFFICE OF RESEARCH AND DEVELOPMENT

- *Health and Environmental Effects Profiles*
- *Health Issues Assessments, Health Assessment Documents*
- *Methodology for Evaluating Potential Carcinogenicity in Support of Reportable Quantity Adjustments Pursuant to CERCLA*
- *Health Effects Assessment Summary Tables*
- Integrated Risk Information System ("IRIS") database

OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES

- *Federal Register* publications of additions to the Toxic Release Inventory ("TRI") and of Toxic Substances Control Act significant new use rules
- FIFRA Scientific Advisory Panel recommendation
- *Carcinogenicity Peer Reviews* of pesticides

OFFICE OF WATER

- *Ambient Water Quality Criteria*
- Drinking Water Criteria
- Drinking water regulations published in the *Federal Register*
- Drinking water *Health Advisories*

US EPA

1986 Guidelines for Carcinogen Risk Assessment

1. **Evidence in humans**
   Evidence in animals
   - Sufficient evidence of carcinogenicity
   - Limited evidence of carcinogenicity
   - Inadequate evidence of carcinogenicity
   - No data
   - No evidence
   - Evidence suggesting lack of carcinogenicity

2. Consider whole body of evidence, including other relevant data, to assign overall classification.

- Group A– Human carcinogen
- Groups B1 and B2 – Probable human carcinogen
- Group C – Possible human carcinogen
- Group D – Not classifiable as to human carcinogenicity
- Group E – Evidence for noncarcinogenicity for humans

US EPA

1986 Guidelines for Carcinogen Risk Assessment

Human data

Sufficient evidence of carcinogenicity: indication that "there is a causal relationship between the agent and human cancer."

Animal data

Sufficient evidence of carcinogenicity: indication that "there is an increased incidence of malignant tumors or combined malignant and benign tumors: (a) in multiple species or strains; or (b) in multiple experiments (e.g., with different routes of administration or using different dose levels); (c) to an unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age at onset. "

US EPA

Cancer Guidelines Update:
1996 Draft Proposed Guidelines for Carcinogen Risk Assessment

- All relevant hazard evidence, including mechanistic and other relevant data, is weighed in one step. Agents are classified as to overall human carcinogenic potential.

- Narrative format

- Descriptors:
  Known/Likely
  Cannot be determined
  Not likely

US EPA

1991 Guidelines for Developmental Toxicity Risk Assessment

Criteria for the minimum evidence necessary to conduct a hazard identification/dose-response evaluation for developmental toxicity:

Human Data

> *"Sufficient Human Evidence*: This category includes data from epidemiologic studies (e.g., case control and cohort) that provide convincing evidence for the scientific community to judge that a causal relationship is or is not supported. A case series in conjunction with strong supporting evidence may also be used. Supporting animal data may or may not be used."

Animal data

> *"Sufficient Experimental Animal Evidence/Limited Human Data*: The category included data from experimental animal studies and/or limited human data that provide convincing evidence for the scientific community to judge if the potential for developmental toxicity exists. The minimum evidence necessary to judge that a potential hazard exists generally would be data demonstrating an adverse developmental effect in a single, appropriate, well-conducted study in a single experimental animal species. The minimum evidence needed to judge that a potential hazard does not exist would include data from appropriate, well-conducted laboratory animal studies in several species (at least two) which evaluated a variety of the potential manifestations of developmental toxicity and showed no developmental effects at doses that were minimally toxic to the adult."

US EPA

1996 Risk Assessment Guidelines for Reproductive Toxicity

Criteria for the minimum evidence necessary to conduct a hazard identification/dose-response evaluation for reproductive toxicity:

Human data

"Sufficient Human Evidence: This category includes agents for which there is convincing evidence from epidemiologic studies (e.g., case control and cohort) to judge whether exposure is causally related to reproductive toxicity. A case series in conjunction with other supporting evidence also may be judged as Sufficient Evidence. An evaluation of epidemiologic and clinical case studies should discuss whether the observed effects can be considered biologically plausible in relation to chemical exposure."

Animal data

"Sufficient Experimental Animal Evidence/Limited Human Data: This category includes agents for which there is sufficient evidence from experimental animal studies and/or limited human data to judge if a potential reproductive hazard exists. Generally, agents that have been tested according to EPA's two-generation reproductive effects test guidelines (but not limited to such designs) would be included in this category. The minimum evidence necessary to determine if a potential hazard exists would be data demonstrating an adverse reproductive effect in a single appropriate, well-executed study in a single test species. The minimum evidence needed to determine that a potential hazard does not exist would include data on an adequate array of endpoints from more than one study with two species that showed no adverse reproductive effects at doses that were minimally toxic in terms of inducing an adverse effect. Information on pharmacokinetics, mechanisms, or known properties of the chemical class may also strengthen the evidence."

US EPA

Working Procedures

Agency-wide guidelines for cancer, developmental and reproductive toxicity risk assessment are followed by all scientific staff conducting human health risk assessments.

Peer Review

Science Advisory Board

Agency-wide peer review of all **major** scientifically-based work products. The level of external peer review a given work product receives is determined on a case-by-case basis, and may be carried out by individuals, *ad hoc* panels, or standing advisory committees.

External peer reviewers are scientists drawn from around the U.S. that possess relevant expertise.

Office of Water defines "major" work products as documents that satisfy one of the following:

- Support major regulatory decisions or policy/guidance of major impact
- Establish a significant precedent, model or methodology
- Address controversial issues
- Focus on significant emerging issues
- Have significant cross-Agency/inter-Agency implications
- Involve a significant investment of Agency resources
- Consider an innovative approach for a previously defined problem/process/methodology
- Satisfy a statutory or other legal mandate for peer review

OOD AND D ADMINISTRATION

Chemicals listed under Proposition 65 through the authoritative bodies mechanism:

FDA is the sole basis for listing:
FDA is the partial basis for listing: **1**

FDA

Risk Assessment

carcinogenic, reproductive and developmental hazards.

(Toxicological Principles for Safety Assessment of Direct Food Additives and Color Additives used in

FDA

Working Procedures

information and assess the weight of evidence, using guidance provided in the Redbook II. Expert

(Cancer Assessment Committee, Quantitative Risk Assessment Committee) are used to make hazard

Peer Review

External peer review is obtained through committees

Committee, drawn from around the U.S. with relevant expertise.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)

Chemicals listed under Proposition 65 through the authoritative bodies mechanism:

IARC is the sole basis for listing: **57**

IARC is the partial basis for listing: **3**

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Authoritative, independent assessments by international experts.

IARC Handbooks of Cancer Prevention

Authoritative, critical reviews and evaluations of evidence by international experts on the cancer preventive and other relevant properties (such as reproductive and developmental toxicity and cancer causation) of agents.

IARC

Criteria for evaluating the level of evidence of carcinogenicity:

1. **Evidence in humans**
   Evidence in animals
   sufficient evidence of carcinogenicity
   limited evidence of carcinogenicity
   inadequate evidence of carcinogenicity
   evidence suggesting lack of carcinogenicity

   Other relevant data
   (including mechanistic data, metabolism and pharmacokinetic information, genetic toxicology data, preneoplastic lesions, tumor pathology, physicochemical parameters, and structure-activity relationships)

The strength of the evidence supporting a particular mechanism is assessed as:

weak
moderate
strong

IARC (CONT.)

2. **Consider body of evidence as a whole, to assign overall evaluation of the carcinogenicity of an agent to humans.**

Group 1 – The agent is carcinogenic to humans
Group 2A – The agent is probably carcinogenic to humans
Group 2B – The agent is possibly carcinogenic to humans
Group 3 –The agent is not classifiable as to its carcinogenicity to humans
Group 4 – The agent is probably not carcinogenic to humans

IARC

Definitions of sufficient evidence of carcinogenicity

Human data

"*Sufficient evidence for carcinogenicity*: The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer studies in which chance, bias and confounding could be ruled out with reasonable confidence."

Animal data

"Sufficient evidence for carcinogenicity: The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasm in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset."

IARC

Evaluation of reproductive and developmental effects

"the adequacy of epidemiological studies of toxic effects, including reproductive outcomes and genetic and related effects in humans, is evaluated by the same criteria as are applied to epidemiological studies of cancer.

For each of these studies, the adequacy of the reporting of sample characterization is considered and, where necessary, commented upon. The available data are interpreted critically according to the end-points used.

The doses and concentrations used are given, and, for *in vitro* experiments, mention is made of whether the presence of an exogenous metabolic system affected the observations.

For *in vivo* studies, the route of administration and the formulation in which the agent was administered are included. The dosing regimens, including the duration of treatment, are also given.

Genetic data are given as listings of test systems, data and references; bar graphs (activity profiles) and corresponding summary tables with detailed information on the preparation of genetic activity profiles are given in appendices. Genetic and other activity in humans and experimental mammals is regarded as being of greater relevance than that in other organisms. The *in vitro* experiments providing these data must be carefully evaluated, since there are many trivial reasons why a response to one agent may be modified by the addition of another."

IARC

Working Procedures

International Working Groups of experts are convened by IARC to formulate critical reviews and evaluations of evidence to be included in the *Monographs* and *Handbooks*. Experts on cancer, as well as reproductive and developmental effects, are members of the Working Groups for the *Handbook* series.

Members of a Working Group are asked to serve as individual scientists, and not as representatives of any organization, government, or industry.

Nominees of national and international agencies and industrial associations may be invited to the Working Group meetings as observers.

Peer Review

Ad hoc panels of expert scientists drawn from around the world prepare and review the *Monographs* and *Handbooks*, in cooperation with IARC staff. Sections of the document are written by a subset of the Working Group, and then peer reviewed by other expert members of the Working Group.

NATIONAL TOXICOLOGY PROGRAM (NTP)

Chemicals listed under Proposition 65 through the authoritative bodies mechanism:

NTP is the sole basis for listing: **32**

NTP is the partial basis for listing: **4**

NTP

- National Institutes of Health's National Institute of Environmental Health Sciences
- National Institutes of Health's National Cancer Institute
- Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health
- Food and Drug Administration's National Center for Toxicological Research

NTP Documents

- Technical Reports
- Toxicity Reports
- other study reports (developmental and reproductive toxicity studies)
- Report on Carcinogens

NTP

Guidance and criteria for assessing evidence of carcinogenicity

1986 Classification Scheme used in the NTP Technical Reports for assessing the strength of the evidence of carcinogenicity for each separate experiment (sex and species):

Clear evidence
Some evidence
Equivocal evidence
No evidence
Inadequate study of carcinogenic activity

Positive findings (clear evidence and some evidence) are taken by NTP to mean that the compound is carcinogenic for laboratory animals under the conditions of the study, and that exposure to the chemical has the potential for hazard to humans.

NTP (CONT.)

1997 Criteria used in the NTP 1998 Report on Carcinogens are similar to IARC's for evaluating carcinogens with respect to the types of information examined and the relative "value" that is placed on human, animal and other relevant data in the overall assessment.

Known to be human carcinogens

"There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer."

Reasonably anticipated to be human carcinogens

"There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded, or"

"There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant and/or combined benign and malignant tumors: (a) in multiple species or at multiple tissue sites, or (b) by multiple routes of exposure, or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or"

"There is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Annual or Biennial Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans."

"Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore reasonably be anticipated not to cause cancer in humans."

NTP

Reproductive and Developmental Toxicology

NTP is a recognized leader in the field, developing a wide range of techniques --- for example, the Continuous Breeding Protocol.

NTP is in the process of establishing the Center for the Evaluation of Risks to Human Reproduction.

NTP

Working Procedures

- The program is administered by the NTP Director, who is the Director of NIEHS.
- Primary program oversight (research and testing needs, priority settings, policy) is provided by the NTP Executive Committee, composed of the heads of Federal research and regulatory agencies.
- Primary scientific oversight is provided by the NTP Board of Scientific Counselors and its Technical Reports Review Subcommittee.
- NTP performs and evaluates laboratory research in experimental animals, and publishes results and assessments of these studies.
- These studies undergo internal and/or external peer review by the NTP Board of Scientific Counselors, subcommittees of the Board, or *ad hoc* reviewers.
- Proposed changes (additions, modifications, delistings) to the NTP Report on Carcinogens undergo a series of reviews by internal and external review groups, committee work groups, and subcommittees, and are subject to additional public comment periods.

Peer Review

NTP has many levels of internal and external peer review.

External peer review

- NTP Board of Scientific Counselors
- Technical Reports Review Subcommittee,
- Report on Carcinogens Subcommittee
- *ad hoc* reviewers

Expert peer reviewers are scientists drawn from around the U.S. and represent a broad range of expertise.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH)

Chemicals listed under Proposition 65 through the authoritative bodies mechanism:

NIOSH is the sole basis for listing: **7**

NIOSH is the partial basis for listing: **4**

NIOSH Documents

- *Criteria for a Recommended Standard* documents
- *Current Intelligence Bulletins*
- *Alerts*
- *Special Hazard Review*
- *Occupational Hazard Assessments*
- *Technical Guidelines*
- NIOSH List of Potential Occupational Carcinogens

NIOSH

NIOSH criteria for evaluation of the carcinogenicity of agents:
1989 OSHA Code of Federal Regulations Title 9, part 1990.

Definitions of potential occupational carcinogens §1990.112

(a) ***Category I Potential Carcinogens***. A substance shall be identified, classified, and regulated as a Category I Potential Carcinogen, upon scientific evaluation, the Secretary determines that the substance meets the definition of a potential occupational carcinogen in (i) humans, or (ii) in a single mammalian species in a long-term bioassay where the results are in concordance with some other scientifically evaluated evidence of a potential carcinogenic hazards, or (iii) in a single mammalian species in an adequately conducted long-term bioassay in appropriate circumstances where the Secretary determines the requirement for concordance is not necessary. Evidence of concordance is any of the following: positive results from independent testing in the same or other species, positive results in short-term tests, or induction of tumors at injection or implantation sites.

(b) ***Category II Potential Carcinogens***. A substance shall be identified, classified, and regulated as a Category II Potential Carcinogen if, upon scientific evaluation, the Secretary determines that: (i) the substance meets the criteria set forth in §1990.112(a), but the evidence is found by the Secretary to be only "suggestive"' or (ii) the substance meets the criteria set forth in §1990.112(a) in a single mammalian species without evidence of concordance.

NIOSH

NIOSH 1994 Reproductive Hazards in the Workplace. Bibliography

Specific adverse reproductive outcomes of concern include:

- reduced fertility
- transplacental carcinogenesis
- mutagenic effects in eggs or sperm
- miscarriages
- birth defects
- low birth weight
- learning disabilities and other behavioral disorders in children
- menstrual disorders
- altered libido

NIOSH

Working Procedures

NIOSH develops and recommends occupational safety and health standards and develops criteria to protect the health of workers.

NIOSH reviews the available literature, evaluates the hazard, and renders a recommendation to OSHA or the Mine and Safety and Health Administration for use in promulgating standards.

Peer Review

NIOSH recommendations on the identification, classification or regulation of a chemical can, at the request of the Secretary of Labor, undergo review by a scientific review panel convened by either NIOSH, the National Cancer Institute, or the National Institute of Environmental Health Sciences. Review panel members must have expertise in appropriate disciplines, and be employed in the U.S.

A chemical is ***formally identified*** by an authoritative body if the regulatory requirements for (1) *identification*, and (2) *formality* have both been satisfied.

Requirements for *identification* consist of written documentation of the authoritative body's conclusion that the chemical is causing cancer or reproductive toxicity, as evidenced by one of three criteria being met:

- inclusion on a list of chemicals causing cancer or reproductive toxicity; or
- a report which concludes that the chemical causes cancer or reproductive toxicity; or,
- was otherwise identified as causing cancer or reproductive toxicity in a document indicating that the identification of the chemical is a final action.

Requirements for *formality* consist of specific and accurate identification of the chemical in a list, report or document, which meets one of the following conditions:

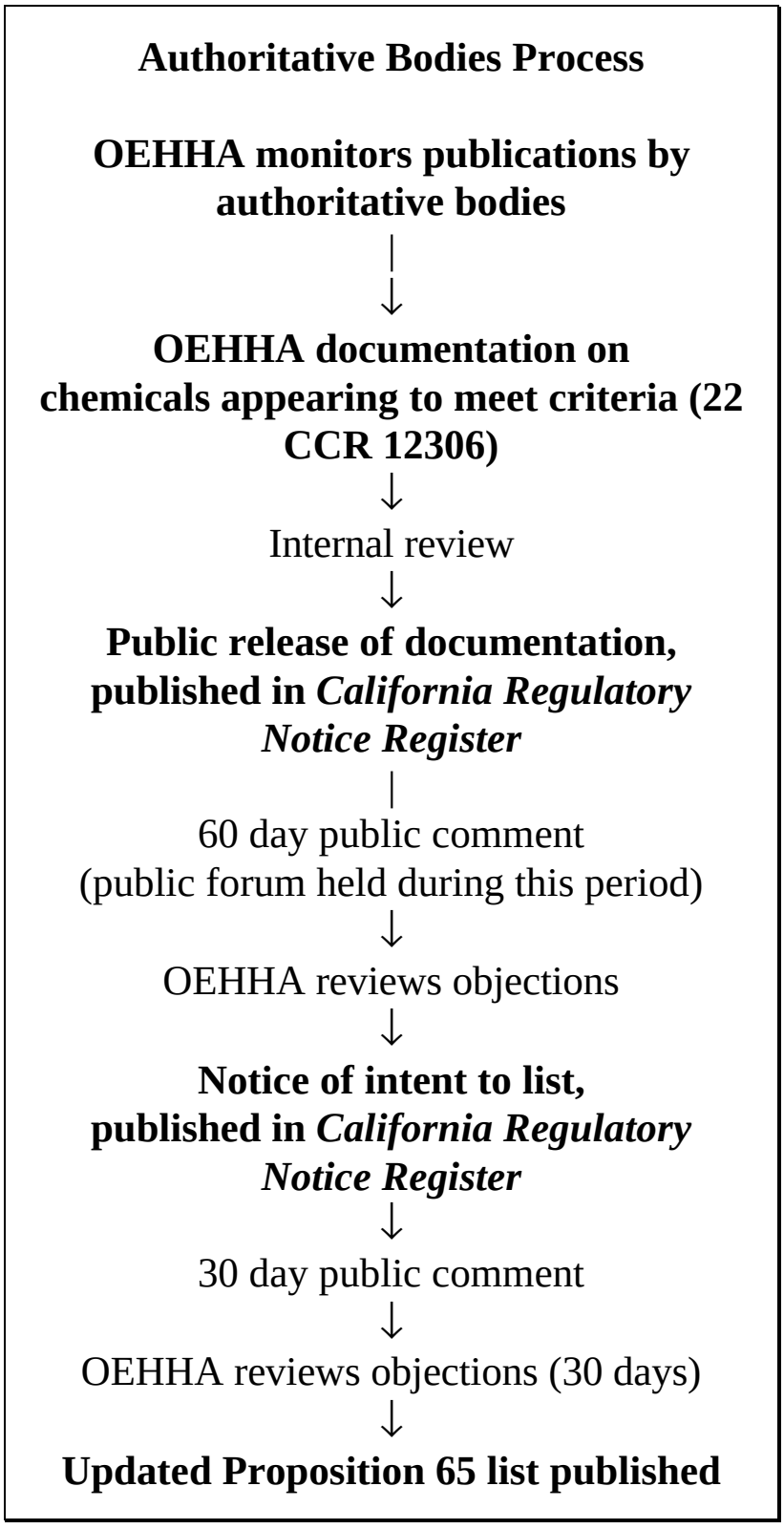
- review by an advisory committee in a public meeting, if required; or
- subject of public review and comment prior to issuance; or
- published in a publication such as the *Federal Register* for an authoritative body which is a federal agency; or
- signed, where required, by the chief administrative officer of the authoritative body or a designee; or
- adoption as a final rule by the authoritative body; or,
- otherwise set forth in an official document utilized by the authoritative body for regulatory purposes.

Scientific Criteria

In addition to the requirements for formal identification, there must be *sufficient evidence* for the identification of the chemical "as causing cancer" or "as causing reproductive toxicity."

Sufficiency of evidence of carcinogenicity includes either sufficient evidence from human studies (*i.e.*, evidence indicating a causal relationship between the chemical and cancer), or sufficient evidence from animal studies *(i.e.*, increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments, or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset).

Sufficiency of evidence of reproductive toxicity includes either human studies indicating a causal relationship between the chemical and reproductive toxicity, or animal studies indicating that there are sufficient data -- taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity -- indicating that an association between adverse reproductive effects in humans and the agent in question is biologically plausible.


Authoritative Bodies Process
OEHHA monitors publications by authoritative bodies
OEHHA documentation on chemicals appearing to meet criteria (22 CCR 12306)
Internal review
Public release of documentation, published in California Regulatory Notice Register
60 day public comment
(public forum held during this period)
OEHHA reviews objections
Notice of intent to list, published in California Regulatory Notice Register
30 day public comment
OEHHA reviews objections (30 days)
Updated Proposition 65 list published

US EPA 1986 (*and Proposed 1996*) and IARC Carcinogen Classification Schemes *Versus* 22 CCR 12306 Criteria[a]

Level of Evidence	US EPA Category 1986 Guidelines	*US EPA Category 1996 Proposed Guidelines*	IARC Category	Meets 22 CCR 12306 Criteria?
1. Sufficient evidence from epidemiological studies	Human carcinogen A	*Known/Likely*	Carcinogenic to humans 1	Yes
2. In exceptional cases, less than sufficient evidence in humans, with sufficient evidence in animals and strong evidence in humans that the agent acts through a relevant mechanism of carcinogenicity	Probable human carcinogen B1 or B2	*Known/Likely*	Carcinogenic to humans 1	Yes
3. Limited evidence from epidemiological studies with sufficient evidence from animal studies	Probable human carcinogen B1	*Known/Likely*	Probably carcinogenic to humans 2A	Yes
4. Sufficient evidence from animal studies with strongly supportive evidence from other relevant studies	Probable human carcinogen B2	*Known/Likely*	Probably carcinogenic to humans 2A	Yes
5. Limited evidence from epidemiological studies with strong supporting data	Probable human carcinogen B1	*Known/Likely*	Probably carcinogenic to humans 2A	No
6. Sufficient evidence from animal studies	Probable human carcinogen B2	*Known/Likely*	Possibly carcinogenic to humans 2B	Yes
7. Limited evidence from animal studies with strongly supportive evidence from other relevant studies	Possible human carcinogen C	*Known/Likely*	Possibly carcinogenic to humans 2B	No
8. Limited evidence from epidemiological studies with no or inadequate supporting data	Probable human carcinogen B1	*Cannot be determined?*	Possibly carcinogenic to humans 2B	No
9. Limited evidence from animal studies with no or inadequate supporting data	Possible human Carcinogen C	*Cannot be determined*	Not classifiable as to its carcinogenicity to humans 3	No
10. Inadequate evidence from	Not classifiable as	*Cannot be*	Not classifiable as to	No

epidemiological animal or other relevant studies	to human carcinogenicity D	*determined*	its carcinogenicity to humans 3	
11. Sufficient evidence from animal studies, with sufficient data to show that these studies are not relevant to humans	?	*Not Likely?*	Not classifiable as to its carcinogenicity to humans 3	No?
12. All available evidence suggests lack of carcinogenicity	Evidence of non-carcinogenicity for humans E	*Not Likely*	Probably not carcinogenic to humans 4	No

[a] 51 Federal Register 33992

VI Chemicals listed as "known to cause reproductive toxicity" via the authoritative bodies mechanism

Listings under Proposition 65: 193
Listings via the authoritative bodies mechanism: 21

Chemical	Toxicity Endpoint	Authoritative Body	Supporting documents[1]	Date listed
o,p'-DDT	developmental female male	NIOSH/ EPA	NIOSH Occupational Safety and Health Guideline; EPA *Health Effects Assessment* (ORD)	5/15/98
p,p'-DDT	developmental female male	NIOSH/ EPA	NIOSH Occupational Safety and Health Guideline; EPA *Health Effects Assessment* (ORD)	5/15/98
m-Dinitrobenzene	male	EPA	*Federal Register*, addition to Toxic Release Inventory (OPPTS)	7/1/90
o-Dinitrobenzene	male	EPA	*Federal Register*, addition to Toxic Release Inventory (OPPTS)	7/1/90
p-Dinitrobenzene	male	EPA	*Federal Register*, addition to Toxic Release Inventory (OPPTS)	7/1/90
Endrin	developmental	EPA	Drinking Water Criteria (OW)	5/15/98
Epichlorohydrin	male	EPA	*Health Effects Document* (ORD)	9/1/96
Ethylene dibromide	developmental male	NIOSH/ EPA	NIOSH *Criteria for Recommended Standard*; EPA *Health Effects Assessment* (ORD)	5/15/98
Ethylene glycol mono-ethyl ether acetate	developmental male	NIOSH	NIOSH *Criteria for Recommended Standard*	1/1/93
Ethylene glycol monomethyl ether acetate	developmental male	NIOSH	NIOSH *Criteria for Recommended Standard*	1/1/93
Ethylene thiourea	developmental	NIOSH	Special Hazard Review	1/1/93
Hexamethylphos-phoramide	male	EPA	*Federal Register*, TSCA significant new use rule (OPPTS)	10/1/94
Mercury and mercury compounds	developmental	EPA	*Health Issues Assessment* (ORD)	7/1/90
Metham sodium	developmental	EPA	*Federal Register*, addition to Toxic Release Inventory (OPPTS)	5/15/98
Nickel carbonyl	developmental	EPA	*Health Assessment Document* (ORD)	9/1/96
Nitrofurantoin	male	NTP	NTP Technical Report	4/1/91

(… continued)

[1] For US EPA documents, the current name of the US EPA parent office generating the publication is provided in parentheses – that is, the Office of Water (OW), Office of Prevention, Pesticides and Toxic Substances (OPPTS), or Office of Research and Development (ORD).

VII Chemicals listed as "known to cause cancer" via the authoritative bodies mechanism

Total listings under Proposition 65: 448
Listings via the authoritative bodies mechanism: 143

Chemical	Authoritative Body	Supporting Documents[2]	Date of Listing
A-alpha-C (2-Amino-9H-pyrido[2,3-b]indole)	IARC	IARC Monograph	1/1/90
Acetamide	IARC	IARC Monograph	1/1/90
Acifluorfen	EPA	Health Advisory Summaries (OW); *Federal Register*, Food tolerance notice (OPPTS)	1/1/90
Acrylamide	EPA/IARC	US EPA IRIS; IARC Monograph	1/1/90
Allyl chloride	EPA	*Hazard Assessment Document* (ORD)	1/1/90
p-Aminoazobenzene	IARC	IARC Monograph	1/1/90
1-Amino-2,4-dibromoanthraquinone	NTP	NTP Technical Report	8/26/97
Aniline	EPA	IRIS	1/1/90
Aniline hydrochloride	EPA	IRIS	5/15/98
Antimony oxide (Antimony trioxide)	IARC	IARC Monograph	10/1/90
Azacitidine	IARC	IARC Monograph	1/1/92
Azobenzene	EPA	IRIS	1/1/90
Benzofuran	NTP	NTP Technical Report	10/1/90
Benzyl chloride	IARC	IARC Monograph	1/1/90
Betel quid with tobacco	IARC	IARC Monograph	1/1/90
2,2-Bis(bromomethyl)-1,3-propanediol	NTP	NTP Technical Report	5/1/96
Bitumens, extracts of steam-refined and air refined	IARC	IARC Monograph	1/1/90
Bracken fern	IARC	IARC Monograph	1/1/90
Bromodichloromethane	EPA	*Health Effects Assessment Summary Tables*	1/1/90
Bromoform	EPA	IRIS	4/1/91
Butylated hydroxyanisole	IARC	IARC Monograph	1/1/90
C.I. Acid Red 114	NTP	NTP Technical Report	7/1/92
C.I. Direct blue 15	IARC	IARC Monograph	10/1/92
C.I. Direct blue 218	NTP	NTP Technical Report	10/1/92

[2]For US EPA documents, the current name of the US EPA parent office generating the publication is provided in parentheses – that is, the Office of Water (OW), Office of Prevention, Pesticides and Toxic Substances (OPPTS), or Office of Research and Development (ORD).
IRIS stands for the Integrated Risk Information System, a US EPA database available electronically.

Workshop presentation - "Other bodies suggested by the public for designation as 'authoritative'"

Marlissa Campbell, OEHHA RCHAS Reproductive Toxicology Unit

Additional Bodies Suggested by the Public for Designation as 'Authoritative'

program	Agency for Toxic Substances and Disease Registry	Health Canada; and Environment Canada	The International Programme on Chemical Safety
parent organization	U.S. Department of Health & Human Services	Government of Canada	World Health Organization (executive organization)
origin of program	Superfund Amendments and Reauthorization Act of 1986	Canadian Environmental Protection Act, 1988	Stockholm Conference on the Environment, 1972
document series	Toxicological Profiles	Priority Substances List Assessment Reports	Environmental Health Criteria
number of agents	priority list of 275 substances; 161 reviews and 44 updates complete	69 chemicals designated; 44 reviews complete	176 documents; reviews of approximately 190 chemicals
guidelines	guidelines for document preparation in Federal Register	published principles for designation of 'toxic'	documents on principles of assessment are produced as part of the series
peer review	internal and external peer reviewers listed in each document	internal and external peer reviewers identified in each document	a task group of experts meets to review and revise the draft document

Workshop presentation - "Scientific criteria for 'as causing cancer or reproductive toxicity' in 22 CCR 12306"

Jim Donald, Chief, OEHHA RCHAS Reproductive Toxicology Unit

Scientific criteria for "as causing cancer or reproductive toxicity" in 22 CCR 12306

12306(e) For purposes of this section, "as causing cancer" means that either of the following criteria have been satisfied:

(1) Sufficient evidence of carcinogenicity exists from studies in humans. For purposes of this paragraph, "sufficient evidence" means studies in humans indicate that there is a causal relationship between the chemical and cancer.

(2) Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, "sufficient evidence" means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset.

12306(g) For purposes of this section, "as causing reproductive toxicity" means that either of the following criteria have been satisfied:

(1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or

(2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.

Excerpts from the "Final Statement of Reasons, 22 California Code of Regulations Division 2. Section 12306 - Chemicals Formally Identified by Authoritative Bodies."

Purpose of Final Statement of Reasons

This final statement of reasons sets forth the reasons for the final language adopted by the Agency section 12306, and responds to the objections and recommendations submitted regarding that section as originally proposed... .

Subsection (e)

Subsection (e) provides that, for purposes of section 12306, the phrase "as causing cancer" means that either of two scientific criteria have been satisfied. Generally, the authoritative body may rely on either studies in humans or studies in animals. These criteria are consistent with the criteria the Panel presently uses in evaluating chemicals for listing. The Panel utilizes the [U.S.] EPA's Classification Scheme for Categorizing Weight of Evidence for Carcinogens From Human and Animal Studies (51 Fed. Reg. 33999 (Sept. 24, 1986)). The same, or substantially similar criteria have been adopted by many regulatory agencies and scientific organizations involved in hazard identification. The use of these criteria will ensure that the standards applied by an authoritative body are the same as or substantially similar to those used by the Panel to evaluate chemicals.

...it is not the intention of the Agency in adopting this regulation to substitute its scientific judgment for the judgment of the authoritative body where sufficient evidence exists. Thus, if there are four animal studies on a particular chemical, two of them positive and two of them negative, and the authoritative body concludes on the basis of the positive tests that the chemical causes cancer, the Agency does not intend to revisit the issue. Thus, if an authoritative body properly applies a strength-of-the-evidence approach, the Agency will not substitute its judgment on the basis of negative data, unless new data not considered by the authoritative body clearly established that there is not sufficient evidence in animals or humans.

On the other hand, where there is in fact an insufficient number of positive animal or human studies, but the authoritative body has concluded anyway that the chemical causes cancer, the Agency will be prevented by the regulation from bringing the chemical to the list. The Agency will not completely defer to the authoritative body, and will at least determine that the body relied upon the requisite human or animal studies.

Excerpts from the "Final Statement of Reasons, 22 California Code of Regulations Division 2. Section 12306 - Chemicals Formally Identified by Authoritative Bodies."
(continued)

Subsection (g)

Subsection (g) provides that, for purposes of section 12306, the phrase "as causing reproductive toxicity" means that either of two scientific criteria have been satisfied. Generally, the authoritative body may rely on either studies in humans or studies in animals.

Paragraph (g) (1) describes the criteria for determining that a chemical causes reproductive toxicity where the authoritative body relied on studies in humans. As with carcinogens discussed above, the proposed regulation requires that sufficient evidence exist from such studies, in that studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity.

Paragraph (g) (2) describes the criteria for determining that a chemical causes reproductive toxicity where the authoritative body relied on studies in animals for its identification of a chemical as a reproductive toxicant. Again, the proposed regulation requires that sufficient evidence exists from such studies. "Sufficient evidence" is defined to mean that there is sufficient data, which take into account the adequacy of the experimental design and other specified parameters, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible. This is consistent with the criteria utilized by the Panel when it evaluates reproductive hazards.

It is not the intention of the Agency to substitute its scientific judgment for that of the authoritative body. The Agency's inquiry will be limited to whether the authoritative body relied on scientific data in an amount sufficient to conclude that the chemical causes reproductive toxicity. The Agency does not intend by this section to go behind the studies relied upon by the authoritative body to determine their scientific validity. Because the body is considered authoritative, and the body utilizes the same or substantially the same criteria as set forth in subsection (g), it will be assumed that the data relied upon is scientifically valid. The Agency will look to determine whether the authoritative body relied upon animal or human data in an amount sufficient to satisfy the criteria. If so, the chemical will be proposed for listing.

Criteria specified in the 1991 U.S. EPA guidelines for the minimum evidence necessary to conduct a hazard identification/dose-response evaluation for developmental toxicity

Human Data

"*Sufficient Human Evidence*: This category includes data from epidemiologic studies (e.g., case control and cohort) that provide convincing evidence for the scientific community to judge that a causal relationship is or is not supported. As case series in conjunction with strong supporting evidence may also be used. Supporting animal data may or may not be used."

Animal data

"*Sufficient Experimental Animal Evidence/Limited Human Data*: The category included data from experimental animal studies and/or limited human data that provide convincing evidence for the scientific community to judge if the potential for developmental toxicity exists. The minimum evidence necessary to judge that a potential hazard exists generally would be data demonstrating an adverse developmental effect in a single, appropriate, well-conducted study in a single experimental animal species. The minimum evidence needed to judge that a potential hazard does not exist would included data from appropriate, well-conducted laboratory animals studies in several species (at least two) which evaluated a variety of the potential manifestations of developmental toxicity and showed no developmental effects at doses that were minimally toxic to the adult."

Criteria specified in the 1996 U.S. EPA guidelines for the minimum evidence necessary to conduct a hazard identification/dose-response evaluation for reproductive toxicity

Human data

"*Sufficient Human Evidence:* This category includes agents for which there is convincing evidence from epidemiologic studies (e.g., case control and cohort) to judge whether exposure is causally related to reproductive toxicity. A case series in conjunction with other supporting evidence also may be judged as Sufficient Evidence. An evaluation of epidemiologic and clinical case studies should discuss whether the observed effects can be considered biologically plausible in relation to chemical exposure."

Animal data

"*Sufficient Experimental Animal Evidence/Limited Human Data:* This category includes agents for which there is sufficient evidence from experimental animal studies and/or limited human data to judge if a potential reproductive hazard exists. Generally, agents that have been tested according to EPA's two-generation reproductive effects test guidelines (but not limited to such designs) would be included in this category. The minimum evidence necessary to determine if a potential hazard exists would be data demonstrating an adverse reproductive effect in a single appropriate, well-executed study in a single test species. The minimum evidence needed to determine that a potential hazard does not exist would include data on an adequate array of endpoints from more than one study with two species that showed no adverse reproductive effects at doses that were minimally toxic in terms of inducing an adverse effect. Information on pharmacokinetics, mechanisms, or known properties of the chemical class may also strengthen the evidence."